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ORIGINAL RESEARCH ARTICLE

Risk of stroke in patients with heart failure and sinus rhythm: data from the Swedish Heart Failure Registry

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Abstract

Aims We investigated the 2 year rate of ischaemic stroke/transient ischaemic attack (IS) in patients with heart failure (HF) who were in sinus rhythm (HF-SR) and aimed to develop a score for stratifying risk of IS in this population.

Methods and results A total of 15 425 patients (mean age 71.5 years, 39% women) with HF-SR enrolled in the Swedish Heart Failure Register were included; 28 815 age-matched and sex-matched controls, without a registered diagnosis of HF, were selected from the Swedish Population Register. The 2 year rate of IS was 3.0% in patients and 1.4% in controls. In the patient group, a risk score including age (1p for 65–74 years; 2p for 75–84 years; 3p for ≥85 years), previous IS (2p), ischaemic heart disease, diabetes, hypertension, kidney dysfunction, and New York Heart Association III/IV class (1p each) was generated. Over a mean follow-up of 20.1 (SD 7.5) months, the cumulative incidences (per 1000 person-years) of IS in patients with score 0 to ≥7 were 2.2, 5.3, 8.9, 13.2, 15.7, 20.4, 26.4, and 33.0, with hazard ratios for score 1 to ≥7 (with 0 as reference): 2.4, 4.1, 6.1, 7.2, 9.4, 12.2, and 15.3. The risk score performed modestly (area under the curve 63.7%; $P = 0.4711$ for lack of fit with a logistic model; $P = 0.7062$ with Poisson, scaled by deviance).

Conclusions In terms of absolute risk, only 27.6% of patients had an annual IS incidence of ≤1%. To which extent this would be amenable to anticoagulant treatment remains conjectural. A score compiling age and specific co-morbidities identified HF-SR patients with increased risk of IS with modest discriminative ability.

Keywords Heart failure; Haemorrhagic stroke; Ischaemic stroke; Risk; Prognosis

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Introduction

Heart failure (HF) of any aetiology has been linked to endothelial dysfunction, activation of thrombin-related pathways, hypercoagulability, and inflammation.[1] These mechanisms are known to increase the risk of systemic and venous thromboembolic complications even in the absence of atrial fibrillation (AF) or flutter.[2]

During the first 1 to 6 months after a diagnosis of HF, there is a high risk of ischaemic stroke, which seems to attenuate over time.[3] In a meta-analysis[4] published in 2013, which included 4386 patients from four randomized controlled trials (WASH,[5] WATCH,[6] WARCHEF,[7] and HELAS[8]), the authors found a benefit in using oral anticoagulants compared with aspirin in reducing the risk of stroke but no survival improvement in patients with HF with reduced ejection fraction and sinus rhythm (HFrEF-SR); at the same time, the risk of major bleeding associated with anticoagulant use outweighed the anti-thromboembolic benefit. With the new oral anticoagulants available on the market, however, the risk of bleeding is reported to be lower than previously resported.[9]

The COMMANDER-HF study published in 2018[10] concluded that rivaroxaban gave no benefit for the composite endpoint of death from any cause, myocardial infarction, or stroke in patients with HFrEF-SR and coronary artery disease; however, in a post hoc analysis,[11] the authors found reduced rates of ischaemic stroke as compared with placebo in this population. Very few studies reporting *real-life data* have used risk

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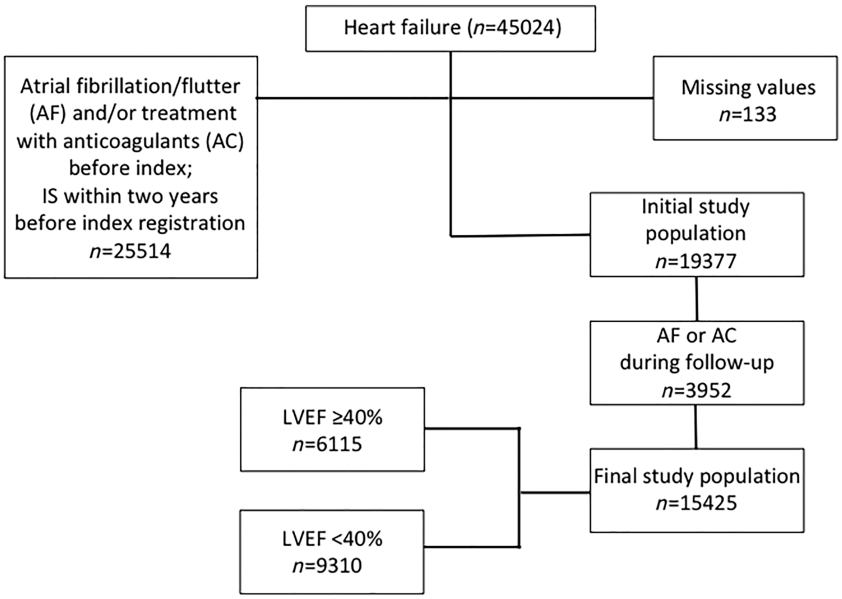
Figure 1 Flow chart showing selection of the study population. LVEF, left ventricular ejection fraction.



stratification models for estimating the incidence of thromboembolic complications in the context of HF-SR. Also, the selection of patients, inclusion criteria, type of treatment, definition of endpoints, and historical period differed between studies. Moreover, definitions of HF have been heterogeneous and based mostly on reported symptoms and only occasionally on left ventricular ejection fraction (LVEF).[12]

The principal aim of this study was to investigate the cumulative 2 year rate of incident ischaemic stroke or transient ischaemic attack (IS), and haemorrhagic stroke (HS) in HF-SR patients registered in the Swedish Heart Failure Register (Swede-HF) in comparison with a matched control population, selected from the Swedish Population Register. A secondary aim was to develop a risk stratification model that would help identify HF-SR patients at high risk for IS.

Methods

Data sources and study cohort

Swede-HF is a nationwide register, launched in 2003.[13] Approximately 80 variables are recorded and the inclusion criterion is clinician-diagnosed HF, irrespective of LVEF. Patients are included either at hospital discharge or as outpatients, either hospital-based or in primary care. Baseline variables are recorded online into a database managed by the Uppsala Clinical Research Centre, Sweden, where the protocol, registration form, and annual report are available.[14] Individual written patient consent is not required, according to Swedish law, but patients are informed about the register and allowed to opt out. Patients who were registered in Swede-HF between 1 January 2003 and 31 December 2013 were eligible for inclusion in the present study if their LVEF had been recorded.

For each case, a maximum of two age-matched and sex-matched controls without HF were randomly selected from the Swedish Population Register. Information regarding use of medication was extracted from the National Drug Register (NDR), covering all prescriptions dispensed from Swedish pharmacies, coded according to the Anatomical Therapeutic Chemical Classification. For controls, information on baseline co-morbidities was collected from the National Patient Register (NPR). In order to obtain as complete information as possible regarding co-morbidities and baseline medication for cases, information from the NPR and from the NDR complemented the data registered in Swede-HF. All diagnoses were coded according to the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10) (*Table S1*). For patients only, creatinine levels were used to obtain estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease study equation.[15] Kidney dysfunction was defined as an eGFR $<$ 60 mL/min/1.73 m^2, and results were supplemented with information on kidney failure reported to the NPR. LVEF measured by echocardiography was recorded at baseline. Baseline was defined as the date of index registration in Swede-HF.

A retrospective matched-cohort study design was used, where 45 024 patients with HF were identified. All study subjects who had ever been diagnosed with AF and/or those who

received treatment with anticoagulants within the previous 6 months from index and/or during the follow-up period were excluded from the study; for details regarding inclusion, see flow chart (*Figure 1*). For inclusion, patients were additionally required to have been free from IS and HS diagnoses within the previous 2 years but could have had any of these diagnoses preceding this period. After exclusions, the final study population (15 425 patients with HF and 28 815 matched controls) was divided into four age groups (<65; 65–74; 75–84; and ≥85 years), as shown in *Table 1*. The present study complies with the Declaration of Helsinki and was approved by the Regional Ethical Review Board of the Swedish Ethical Review Authority (Dnr 026-16).

Outcomes

Outcome was defined as any incident IS (ICD-10 codes G45 and I63) that occurred within the following 2 years after the index registration of HF. Additionally, information on incident HS (ICD-10 codes I61 and I62) was collected. Throughout the course of the study, computed tomography scan has been part of the routine workup of patients with neurological deficit in Sweden; thus, when a diagnosis of stroke is reported in the NPR, it is always coded according to type, that is, ischaemic or haemorrhagic. Cardiovascular and all-cause mortality data were collected from the Cause of Death Register, National Board of Health and Welfare in Sweden.

Risk score

Factors associated with the outcome (IS) in univariate Cox regression ($P < 0.1$) were included in a multivariable regression analysis. A risk score was created by combining those variables that were found to significantly increase the risk of IS. any. The variables were weighted based on hazard ratio (HR) values, as follows: age (1p for 65–74 years; 2p for 75–84 years; 3p for ≥85 years), previous ischaemic heart disease (1p), hypertension (1p), diabetes mellitus (1p), previous IS (2p), kidney dysfunction (1p), and New York Heart Association (NYHA) class III or IV (1p).

Statistics

Data on vital status were censored on 31 December 2015. All data management and statistical analyses were carried out in SAS 9.4; graphics were drawn in R 3.5.3. Significance level was pre-set at $p < 0.05$ unless stated otherwise. Baseline characteristics are presented as counts (per cent) for categorical and as means (standard deviation), or medians (first and third quartiles) for numeric data. Differences between study groups were assessed by χ^2 test for dichotomous and *t*-test for continuous variables. Non-parametric Wilcoxon test was used for comparison of medians.

Crude incidence rates (IRs) of IS by risk score are shown as counts (per cent). Cumulative incidence per 1000 person-years was obtained by Cumulative Incidence Function from Cox proportional hazard model with any cause (but outcome of interest) of death as competing risk. IR per 1000 person-years was calculated under assumption of Poisson distribution. Unadjusted Cox models and logistic regression were used to obtain hazard ratios (HRs) and odds ratios (ORs) with the lowest risk score (0) as reference in order to describe the relationship between risk categories.

The event count was then modelled by logistic (1) and Poisson regression, scaled by deviance (2) in search for the best fit for the data. When appropriate, lack of fit (1) or test of the model form (2) was performed. Akaike information criterion (AIC) (3) was used for model selection.

Model	Expression	Parameter	Test	Required *P*-value/ pre-set evaluation criteria
1. Logit	$(p) = \ln\left(\frac{p}{1-p}\right)$	p is a probability of an event	Lack of fit *C*-statistics	≥0.0565.0–74.0 satisfying; 75.0–84.0 good; 85.0 and higher excellent
2. Poisson	$\mu = E(Y_i)$, $\mathrm{Var}(Y_i) = \varphi\mu$	φ is correction term for overdispersion	Model form	≥0.05
3. AIC	$2k - 2\log(L(\theta\|y))$	k is the number of estimated parameters; $\log(L(\theta\|y))$ is the log-likelihood at its maximum	Quantity of information lost during a statistical procedure	The smallest value is preferred

Table 1 Characteristics of the study population at baseline by age group

Age groups	<65 years			65–74 years		
	Case (n = 4283)	Control (n = 8562)	P-value	Case (n = 3850)	Control (n = 7666)	P-value
Clinical characteristics						
Age, mean (SD)	54.4 (8.9)	54.4 (8.9)	0.9806	69.7 (2.9)	69.7 (2.9)	0.8926
Age, median (Q1, Q3)	57 (50; 61)	57 (50; 61)	0.9732	70 (67; 72)	70 (67; 72)	0.8920
Women, %	1268 (29.6)	2536 (29.6)	0.9871	1316 (34.2)	2626 (34.3)	0.9376
Obesity	297 (6.9)	99 (1.2)	<0.001	211 (5.5)	80 (1.0)	<0.001
Ischaemic heart disease, %	1651 (38.5)	373 (4.4)	<0.001	2164 (56.2)	806 (10.5)	<0.001
Dilated cardiomyopathy, %	904 (21.1)	83 (1.0)	<0.001	359 (9.3)	26 (0.3)	<0.001
Hypertrophic cardiomyopathy, %	78 (1.8)	38 (0.4)	<0.001	42 (1.1)	11 (0.1)	<0.001
Co-morbidities, n (%)						
Hypertension	1530 (35.7)	706 (8.2)	<0.001	1785 (46.4)	1346 (17.6)	<0.001
Valvulopathy	189 (4.4)	18 (0.2)	<0.001	217 (5.6)	33 (0.4)	<0.001
Aortic or mitral						
Diabetes mellitus	971 (22.7)	417 (4.9)	<0.001	1217 (31.6)	594 (7.7)	<0.001
Lung disease	585 (13.7)	278 (3.2)	<0.001	752 (19.5)	384 (5.0)	<0.001
Ischaemic stroke/TIA	126 (2.9)	75 (0.9)	<0.001	264 (6.9)	277 (3.6)	<0.001
Kidney dysfunction	206 (4.8)	61 (0.7)	<0.001	317 (8.2)	70 (0.9)	<0.001
Outcome (2 year follow-up), n (%)						
Ischaemic stroke/TIA	59 (1.4)	38 (0.4)	<0.001	115 (3.0)	92 (1.2)	<0.001
Haemorrhagic stroke	5 (0.1)	8 (0.1)	0.6953	10 (0.3)	12 (0.2)	0.2315
Cardiovascular mortality	104 (2.4)	8 (0.1)	<0.001	189 (4.9)	22 (0.3)	<0.001
All-cause mortality	349 (8.1)	61 (0.7)	<0.001	653 (17.0)	154 (2.0)	<0.001
Per 1000 person-years, IR (95% CI)						
Ischaemic stroke/TIA	7.29 (5.65–9.41)	2.23 (1.62–3.07)	<0.001	16.93 (14.11–20.33)	6.09 (4.97–7.47)	<0.001
Haemorrhagic stroke	0.61 (0.26–1.48)	0.47 (0.24–0.94)	0.6371	1.45 (0.78–2.70)	0.79 (0.45–1.39)	0.1564
Per 1000 person-years, MR (95% CI)						
Cardiovascular mortality	12.76 (10.53–15.47)	0.47 (0.23–0.94)	<0.001	27.41 (23.77–31.61)	1.45 (0.95–2.20)	<0.001
All-cause mortality	42.83 (38.56–47.57)	3.58 (2.78–4.59)	<0.001	94.71 (87.72–102.3)	10.14 (8.66–11.88)	<0.001

Table 1 (continued)

75–84 years			>84 years		
Case (n = 4777)	Control (n = 9079)	P-value	Case (n = 2515)	Control (n = 3508)	P-value
79.7 (2.8)	79.6 (2.8)	0.0763	88.2 (2.9)	87.5 (2.3)	<0.0001
80 (77; 82)	80 (77; 82)	0.0750	88 (86; 90)	87 (86; 89)	<0.001
2009 (42.1)	3934 (43.3)	0.1495	1369 (54.4)	2137 (60.9)	<0.001
123 (2.6)	31 (0.3)	<0.001	11 (0.4)	4 (0.1)	0.0130
2864 (60.0)	1268 (14.0)	<0.001	1403 (55.8)	503 (14.3)	<0.001
196 (4.1)	19 (0.2)	<0.001	35 (1.4)	1 (0.0)	<0.001
31 (0.6)	8 (0.1)	<0.001	14 (0.6)	1 (0.0)	0.0001
2378 (49.8)	2071 (22.8)	<0.001	1282 (51.0)	949 (27.1)	<0.001
364 (7.6)	49 (0.5)	<0.001	160 (6.4)	11 (0.3)	<0.001
1248 (26.1)	788 (8.7)	<0.001	465 (18.5)	290 (8.3)	<0.001
881 (18.4)	514 (5.7)	<0.001	370 (14.7)	184 (5.2)	<0.001
478 (10.0)	528 (5.8)	<0.001	304 (12.1)	263 (7.5)	<0.001
481 (10.1)	111 (1.2)	<0.001	283 (11.3)	70 (2.0)	<0.001
189 (4.0)	203 (2.2)	<0.001	99 (3.9)	79 (2.3)	0.0001
16 (0.3)	47 (0.5)	0.1286	12 (0.5)	13 (0.4)	0.5259
480 (10.0)	127 (1.4)	<0.001	453 (18.0)	128 (3.6)	<0.001
1453 (30.4)	566 (6.2)	<0.001	1333 (53.0)	580 (16.5)	<0.001
24.94 (21.62–28.76)	11.66 (10.17–13.38)	<0.001	30.97 (25.43–37.72)	12.46 (10.00–15.54)	<0.001
2.08 (1.27–3.39)	2.68 (2.01–3.56)	0.3794	3.68 (2.09–6.48)	2.03 (1.18–3.50)	0.1383
62.15 (56.83–67.97)	7.22 (6.07–8.59)	<0.001	138.9 (126.6–152.2)	20.00 (16.82–23.79)	<0.001
188.1 (178.7–198.1)	32.17 (29.63–34.94)	<0.001	408.6 (387.2–431.1)	90.63 (83.55–98.32)	<0.001

Results

Study population

After exclusions, the final study population consisted of 15 425 HF-SR patients and 28 815 age-matched and gender-matched controls (*Figure 1*). The mean age of the patients was 71.5 (SD 13.3) years, and 38.7% were women. Even the youngest patients (<65 years) had a high prevalence of cardiovascular and other disorders. Ischaemic heart disease was present in 38.5%, hypertension in 35.7%, diabetes in 22.7%, and dilated cardiomyopathy in 21.1%. Older patients had a lower prevalence of cardiomyopathy, but more often hypertension, kidney dysfunction, ischaemic heart disease, and a history of IS. The control population had markedly fewer co-morbidities than the HF-SR patients (*Table 1*).

Outcome

During a mean follow-up of 20.1 (SD 7.5) months, 462 (3.0%) patients and 412 (1.4%) controls had an IS, $P < 0.0001$; the corresponding numbers for HS were 43 (0.3%) and 80 (0.3%), $P = 0.983$, while all-cause mortality was 24.6% among patients and 4.7% among controls, $P < 0.0001$.

The crude IS IR per 1000 person-years increased across age groups among both patients and controls; patients < 65 years had an IR of 7.29 (CI 5.65–9.41), while for age-matched controls, the IR was 2.23 (CI 1.62–3.07), $P < 0.0001$. The IR was 30.97 (CI 25.43–37.72) and 12.46 (CI 10.00–15.54) for patients and controls >84 years, respectively, $P < 0.0001$. The IR for HS followed a similar age-related trend, but no significant difference was observed between patients and controls (*Table 1*).

Table 2 Characteristics of the study population and outcomes by left ventricular ejection fraction

LVEF groups	Total (*n* = 15 425)	LVEF ≥ 40% (*n* = 6115)	LVEF < 40% (*n* = 9310)	*P*-value
Clinical characteristics				
Age, mean (SD)	71.5 (13.3)	73.6 (13.1)	70.2 (13.3)	<0.0001
Age, median (Q1, Q3)	73 (63; 82)	76 (66; 83)	72 (62; 81)	<0.001
Women, %	5962 (38.7)	2906 (47.5)	3056 (32.8)	<0.001
Obesity	642 (4.2)	328 (5.4)	314 (3.4)	<0.001
Smoking	2126 (13.8)	686 (11.2)	1440 (15.5)	<0.001
Duration of heart failure				
Up to 6 months	8774 (56.9)	3386 (55.4)	5388 (57.9)	0.0087
>6 months	6543 (42.4)	2686 (43.9)	3857 (41.4)	
Ischaemic heart disease	9443 (61.2)	3758 (61.5)	5685 (61.1)	0.6250
Dilated cardiomyopathy, %	1494 (9.7)	415 (6.8)	1079 (11.6)	<0.001
Hypertrophic cardiomyopathy, %	165 (1.1)	110 (1.8)	55 (0.6)	<0.001
NTproBNP, median (Q1; Q3)	2110 (740; 5805)	1407 (506; 4091)	2632 (982; 7000)	<0.001
NTproBNP (*n* missing)	10 382 (67.3)	4161 (68.0)	6221 (66.8)	
Co-morbidities, n (%)				
Hypertension	9026 (58.5)	4058 (66.4)	4968 (53.4)	<0.001
Valvulopathy (aortic or mitral)	930 (6.0)	421 (6.9)	509 (5.5)	0.0003
Diabetes mellitus	4454 (28.9)	1843 (30.1)	2611 (28.0)	0.0050
Lung disease	2588 (16.8)	1160 (19.0)	1428 (15.3)	<0.001
Ischaemic stroke/TIA	1383 (9.0)	650 (10.6)	733 (7.9)	<0.001
Kidney dysfunction	1583 (10.3)	712 (11.6)	871 (9.4)	<0.001
Baseline medication				
RAS inhibition	13 049 (84.6)	4738 (77.5)	8311 (89.3)	<0.001
Beta-blockers	13 066 (84.7)	4772 (78.0)	8294 (89.1)	<0.001
MRA	4030 (26.1)	1235 (20.2)	2795 (30.0)	<0.001
Platelet inhibitor	11 223 (72.8)	4337 (70.9)	6886 (74.0)	<0.001
Statins	8116 (52.6)	3189 (52.2)	4927 (52.9)	0.3481
Diuretics	11 163 (72.4)	4323 (70.7)	6840 (73.5)	0.0002
Outcome (2 year follow-up), n (%)				
Ischaemic stroke/TIA	462 (3.0)	181 (3.0)	281 (3.0)	0.8353
Time to event, months, median (Q1; Q3)	8.4 (2.6; 16.4)	8.0 (2.5; 16.3)	8.8 (2.8; 17.0)	0.4464
Haemorrhagic stroke	43 (0.3)	23 (0.4)	20 (0.2)	0.0631
Time to event, months, median (Q1; Q3)	10.9 (4.5; 19.5)	11.7 (5.2; 19.5)	10.5 (4.3; 19.3)	0.6612
Cardiovascular mortality	1226 (8.0)	460 (7.5)	766 (8.2)	0.1132
All-cause mortality	3788 (24.6)	1579 (25.8)	2209 (23.7)	0.0031
Per 1000 person-years				
Ischaemic stroke/TIA	18.01 (16.44–19.72)	17.93 (15.50–20.74)	18.05 (16.06–20.29)	0.9436
Haemorrhagic stroke	1.65 (1.23–2.23)	2.25 (1.50–3.39)	1.27 (0.82–1.96)	0.0603
Cardiovascular mortality	47.10 (44.54–49.81)	44.94 (41.01–49.24)	48.51 (45.19–52.06)	0.1954
All-cause mortality	145.5 (141.0–150.2)	154.3 (146.8–162.1)	139.9 (134.2–145.8)	0.0030

MRA, magnetic resonance angiography; NTproBNP, N-terminal pro-brain natriuretic peptide.

Of the patients, 9310 (60.4%) had LVEF < 40% (*Table 2*). Patients with LVEF ≥ 40% (*n* = 6115, 39.6%) were older, more often women, and had a higher co-morbidity burden. Although the all-cause mortality rate in an unadjusted analysis was higher among patients with LVEF ≥ 40% than among patients with LVEF < 40% (25.8% vs. 23.7%, *P* = 0.003), no difference in risk of IS by LVEF was found.

In a multivariable regression of the HF-SR patients without any reported co-morbidity (*n* = 2368; 69% with LVEF < 40%, mean age 65.5 (SD 18.6) years; 31% with LVEF ≥ 40%, mean age 63.5 ± 15.6 years; *P* = 0.013), gender (HR 1.13; CI 0.60–2.25; *P* = 0.72) and LVEF were not independent predictors of IS (HR 0.79; CI 0.39–1.59, *P* = 0.50) in contrast to age (HR 1.07; CI 1.04–1.10, *P* < 0.0001).

Risk score in the patient population

Table 3 shows ORs for IS associated with individual baseline variables. With death as competing risk, an incremental HR for IS was observed for patients with score 1 to ≥7: 2.4, 4.2, 6.0, 7.4, 9.3, 12.4, and 14.9; while the IS cumulative incidence per 1000 person-years was 2.2, 5.3, 9.0, 13.0, 15.9, 19.8, 26.5, and 31.7, respectively. Narrower confidence intervals and lower AIC were obtained by using the Poisson model in comparison with the logistic model (*Figure 2* and *Table 4*). With the use of a χ^2-test, no statistical difference was found between the observed and predicted IS events (*P* = 0.64 for the Poisson model and *P* = 0.30 for the logistic model). The risk score performed modestly (*C*-statistic 63.7%; *P* = 0.47 for lack of fit with a logistic model and *P* = 0.71 with Poisson, scaled by deviance).

Table 3 Odds ratios and corresponding number of points for variables included in the risk score

Tested variables	OR for ischaemic stroke	*P*-value	Risk points
Age			
<65	1.00 (ref.)		0
65–74	2.30 (1.68–3.15)	<0.0001	1
75–84	3.35 (2.50–4.48)	<0.001	2
85 +	4.02 (2.91–5.55)	<0.001	3
Smoking	1.18 (0.98–1.42)	0.0773	0
Co-morbidity			
Ischaemic heart disease	1.53 (1.26–1.87)	<0.001	1
Hypertension	1.58 (1.30–1.92)	<0.001	1
Diabetes mellitus	1.64 (1.36–1.98)	<0.001	1
Ischaemic stroke/TIA	2.51 (1.98–3.18)	<0.001	2
Kidney dysfunction[a]	1.62 (1.35–1.95)	0.0002	1
Left ventricle ejection fraction			
LVEF > 40	1.00 (ref.)		0
LVEF ≤ 40	1.01 (0.84–1.22)	0.9256	0
NYHA class[a]			
I	1.00 (ref.)		0
II	1.11 (0.84–1.48)	0.4650	
III	1.52 (1.14–2.02)	0.0047	1
IV	1.98 (1.39–2.81)	0.0002	

[a]Missing values: kidney dysfunction (0.06%) and NYHA class (0.01%).

Discussion

In this nationwide study, we found that the cumulative risk of IS among HF-SR patients during the first 2 years after index registration was 3%, about twice that of matched controls. The risk of HS, however, was roughly 10 times lower and remarkably similar in patients and controls (0.3%). A risk score compiling age and co-morbidity was shown to identify patients at high risk for IS with moderate discriminative ability.

As expected, the co-morbidity burden differed considerably between cases and controls, with the control population having significantly fewer co-morbidities than the HF-SR patients. Thus, the increased risk of ischaemic stroke is, presumably, the result of a detrimental combination of HF, age, and co-morbidity, and, in fact, very similar to that seen in patients with AF.

Conceivably, owing to worse haemodynamics, patients with low LVEF might have a higher risk of thromboembolic events and ischaemic stroke than patients with HF with preserved ejection fraction (HFpEF). However, our results indicated that patients with LVEF ≥ 40% had rates of ischaemic stroke that were comparable with those of patients with LVEF < 40%. Two additional analyses based on other LVEF categories [(i) LVEF < 30, 30–39, 40–49, and ≥50%; (ii) LVEF < 40, 40–49, and ≥50%] provided similar results (data not shown). A putative explanation for these findings would be that patients with LVEF ≥ 40% were older and had a higher co-morbidity burden, which may have evened out the impact of reduced LVEF on stroke rates. To address this question, a subgroup analysis was performed in the 2368 HF-SR patients without any reported co-morbidity; age, but not LVEF or gender, was found to independently predict the risk of ischaemic stroke. Thus, in accordance with the findings by Abdul-Rahim *et al.*,[16] the study indicates that LVEF has no significant impact on the risk of IS. However, it might be that by excluding patients treated with anticoagulants, we discard from the analysis the patients with severely depressed systolic function who might have gotten anticoagulant treatment based on clinical suspicion, high probability of thrombosis, or diagnosed intracavitary thrombosis.

Similar to AF patients, age and co-morbidity seem to play an essential role in determining the risk of ischaemic stroke even in patients with HF-SR. In the analysis of pooled data from the CHARM-Preserved and I-Preserve trials[16] that included 4676 patients with HFpEF without AF, a risk score based on age, body mass index, NYHA class, history of stroke, and insulin-treated diabetes identified patients at elevated risk of future stroke. This risk score was previously tested on HFrEF patients.[17] However, the definition of stroke did

Figure 2 Performance of risk score: observed and predicted ischaemic stroke events by number of risk points.

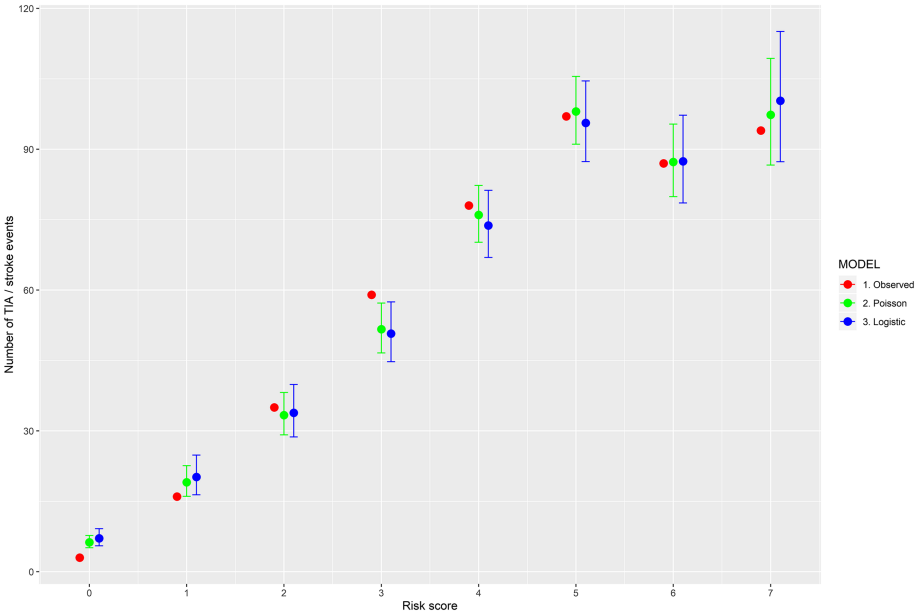


Table 4 Goodness of fit (observed vs. predicted ischaemic stroke/TIA events) by number of risk points according to ordinal logistic model and Poisson, scaled by deviance

Score points	Study population *n* (%)	Observed events *n* (%)	Predicted values	
			Logistic	Poisson
0	707 (4.6)	3 (0.4)	7.0 (5.5–9.1)	6.2 (5.0–7.6)
1	1548 (10.0)	16 (1.0)	20.1 (16.3–24.7)	19.0 (16.0–22.4)
2	2008 (13.0)	35 (1.7)	34.0 (28.8–40.0)	33.5 (29.3–38.2)
3	2329 (15.1)	59 (2.5)	50.6 (44.7–57.4)	51.5 (46.5–57.0)
4	2625 (17.0)	77 (2.9)	73.7 (66.9–81.2)	76.0 (70.3–82.2)
5	2642 (17.1)	98 (3.7)	95.7 (87.5–104.7)	98.1 (91.3–105.5)
6	1881 (12.2)	87 (4.6)	87.4 (78.5–97.2)	87.2 (80.0–95.2)
≥7	1685 (10.9)	94 (5.6)	100.5 (87.5–115.3)	97.5 (87.0–109.4)
AUC			63.7 (61.4–66.1)	
Wald χ^2 (global null hypothesis: $\beta = 0$)			<0.0001	<0.0001
Lack of fit/test of the model form			0.4711	0.7062
Akaike information criterion			53.9	52.0

AUC, area under the curve.

not discriminate between IS and HS; and moreover, about 6% of the patients were on anticoagulant therapy.

In this real-world cohort, neuroimaging for diagnosing stroke was used throughout the course of the study, and accordingly distinguishing between IS and HS was not problematic. Surprisingly, even though the rate of HS showed a clear age-related trend, the risk was similar among HF-SR patients and their controls. Considering the co-morbidity burden of the HF-SR patients, these findings are intriguing, and any potential reasons remain unclear. Nevertheless, it is important to highlight that the rate of cerebral bleeding was very much lower than that of ischaemic stroke in the HF-SR patients < 65 years, while, in terms of absolute risk, only 27.6% of the whole study cohort had an annual incidence of IS of ≤1%.

It has been suggested that in order to justify anticoagulation with warfarin, stroke rates in HF patients must be about 3–5% per year,[18] but with the use of newer, safer oral anticoagulants, stroke rates of ≥0.9% per year may be considered a reasonable limit.[9] Moreover, the recently published results from COMMANDER-HF[11] showed that rivaroxaban reduced rates of ischaemic stroke compared to placebo, with the safety endpoint of fatal/critical bleeding occurring at a similar rate on rivaroxaban and placebo. In this context, a risk score is a valuable instrument in the selection of patients at high risk for IS, who may benefit from anticoagulant treatment.

Even though the risk score in our analysis only performed moderately well, its clinical relevance is supported by the fact that no difference was found between observed and predicted IS events, as shown in the 'take-home figure' (*Figure 2*). Indeed, despite the fact that incidence of IS in HF-SR is relatively low, it certainly cannot be ignored, in particular in the subgroup of patients with a high score, who carry a considerable risk; further studies investigating the benefit of anticoagulant therapy in this category of patients are warranted.

Melgaard *et al*.[19] tested the predictive value of CHA_2DS_2-VASc score for ischaemic stroke, thrombo-embolism, and death in a cohort of Danish HF patients with and without AF; and, similar to the present study, they found that the predictive accuracy for ischaemic stroke was modest (*C*-statistic 0.67 for patients with AF and 0.64 for those without).

We chose not to use a predefined risk score but rather to develop one based on variables shown to significantly affect the probability of ischaemic stroke. However, our final selection of variables turned out to be very similar to the one included in the CHA_2DS_2-VASc score, with the exception of sex category, which was not a predictor in our cohort; instead, kidney dysfunction and NYHA class were included in the score. The risk score predicted better than chance with a *C*-statistic of 0.64, and this value remained unaffected in the sensitivity analysis. While the predictive accuracy is modest, it is still comparable with the one that the CHA_2DS_2-VASc score has shown in patients with AF (*C*-statistic 0.60),[20] notwithstanding the fact that the overall risk for IS in our study cohort is lower than in patients with HF and AF. Even if the proposed score needs to be further validated before it may be adopted for making clinical treatment decisions, it is expected to facilitate design for selection of HF-SR patients for future trials on stroke prevention.

Our study has several strengths but also some evident limitations. It is based on a real-world cohort, the sample size is large, and the definitions of diagnoses and the outcomes are well validated; the use of a matched control group enabled us to estimate absolute risk as well as the relative risk of IS and HS in patients with HF-SR as compared with a background population; the analyses take into consideration the competing risk of death; patients receiving anticoagulants, as well as those with AF prior to HF diagnosis and/or during the follow-up period, were excluded. We cannot rule out that some patients might have had silent AF that had escaped detection; however, this is a common difficulty in clinical praxis. Our study design is also, as other registry-based studies, at risk of being subject to selection bias and confounding variables. Although Swede-HF contains a large number of unique patients with extensive baseline variables, we cannot rule out inaccuracies in recorded data or unmeasured confounding variables. Another limitation is the variation of available treatments and routine praxis over the inclusion period of 10 years and the absence of standardised neuroimaging data. Still, a validation study of the diagnoses reported to the NPR shows a high degree of validity.[21] Some of the reported diagnoses for controls may be underestimated owing to the fact that some patients might only have had contact with the primary care where diagnoses are not reported to the NPR. Finally, the risk score that we propose has not been validated in any other patient cohort but still demonstrates a fair goodness of fit in this population.

One-sentence summary

Patients with HF and sinus rhythm had an increased risk of ischaemic, but not haemorrhagic, stroke that cannot be ignored; a score compiling age and specific co-morbidities identified patients with increased risk of IS, underlining the need of further investigation for stroke prevention in this specific group of patients.

Conflict of interest

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. List of ICD 10-codes and ATC-codes used in the study

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